TO: Dr. Frederic W. Nordsiek

FROM: Dr. Wayne L. Ryan

DATE: February 5, 1973

SUBJECT: Mendicino Grant Application #903

The hypothesis of this application is not clear and the introduction consists of a series of statements which are not tied together. For example, the last paragraph on page 8 doesn't seem to have any relation to the problem.

The documentation in the introduction, specific aims, and methods is very poor. Several hundred papers have been written on catecholamine activation of adenylate cyclase, and he doesn't reference them so as to indicate familiarity.

The first step in the experimental plan is to measure the levels of cyclic AMP in lung and brain of animals treated with nicotine.

The methods section indicates that he plans to use his method (which has not been published and is not adequately described in the proposal) for assaying cyclic AMP.

Aside from the lack of verification of his method, there is little reason for using it. Only a few milligrams of tissue are required for the radioimmunoassay. The samples should be purified before assaying and phosphodiesterase controls used to authenticate that the material measured is cyclic AMP.

The second step in the experimental plan is to measure adenylate cyclase and phosphodiesterase after administration of nicotine.

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The adenylate cyclase method he describes is not his method, but a modification of the method of Krishna and should be referenced. The PDE method is that of Thompson and Appleman. The adenylate cyclase measurement is extremely difficult, and there is no indication that he has actually used it.

If nicotine elevates the level of catecholamines in blood, he can be assured of higher cyclic AMP levels in the tissues. An interesting question is whether nicotine can act directly on adenylate cyclase. That is, is there an adenylate receptor in cells that is responsive to nicotine? This experiment could be conducted in vitro using cell homogenates and would answer the most important question that he asks.

In general, the proposal is poorly written, but the most disturbing part of it is the use of his own methods which have not been reported. Examination of his curriculum vitae would suggest that the problems I have pointed out are due to lack of experience and knowledge of the area.

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